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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/423,042	01/19/00	GUY B	06132/054001

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EXAMINER	
PORTNER, V	
ART UNIT	**PAPER NUMBER**
1645	7

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/423,042	Applicant(s) Guy et al
	Examiner Portner	Group Art Unit 1645

☒ Responsive to communication(s) filed on *Oct 29, 1999* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-18 and 25* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-18 and 25* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *3*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 1-18 and 25 are pending.

Priority

1. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been filed in parent Application No. PCT US98/088909, filed on April 30, 1998.

Information Disclosure Statement

2. The information disclosure statement filed December 6, 1999 has been considered prior to first action.

Drawings

3. This application has been filed with drawings which are acceptable for examination purposes. Please see attached PTO-948 form.

Specification

4. The disclosure is objected to because of the following informalities: At page 20, lines 25-27; page 21, lines 1-2 and

25-27; page 22, lines 4-8, it was noted that brackets are set forth. The use of bracketed information [ ], in a patent application, defines information to be deleted therefrom. Removal of the brackets is requested.

Claim Rejections - 35 U.S.C. § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 25 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for induction of an immune response, does not reasonably provide enablement for the administration of any immunogenic agent in a method of preventing or treating Helicobacter infection. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claimed invention is directed to the use of any Helicobacter immunogenic agent in a method of preventing or

treating Helicobacter infection in any mammal through the administration of the agent mucosally and parenterally.

While the immunogenic agents, by definition, would induce an immune response, the amount administered may be any amount, induce any type of immune response, using any immunogen from any Helicobacter to induce an immune response in any mammal. The immune response need not be a long lasting immune response, nor is the immunogen combined with a pharmaceutical carrier or adjuvant for induction of an enhanced immune response.

The specification does not provide substantive evidence that any immunogenic agent from any Helicobacter would provide for prevention or treatment of Helicobacter infection.

Data obtained from challenge experiments must demonstrate an art recognized standard of improvement over the control in order for the composition to be considered as being useful for treating or preventing infection and disease. This information is essential for the skilled artisan to be able to use the claimed immunogenic agents for their intended purpose of treating or preventing *Helicobacter* infection. Without this demonstration, the skilled artisan would not be able to reasonably predict the outcome of the administration of the claimed immunogenic agents, i.e. would not be able to accurately predict if protective immunity has been induced. Patients with H.pylori infection

produce a diagnostic immune response that is not therapeutic as infection persists.

The prior art teaches that Helicobacter pylori vaccines are unpredictable, specifically, in the type of effect they will have on preventing or treating infection. The ability to reasonably predict the capacity of a single bacterial immunogen, to induce protective immunity is problematic.

In HP WORLD-WIDE, a publication from Brocades Pharma BV Leiderdorp, The Netherlands, February 1992, data was presented stating that immunization does not appear promising. Parenteral immunization of specific pathogen free mice with *H. felis* gave no protection against gastric colonization; previous oral infection only delayed colonization (Heap,K, Australia). The article also taught that "although intra-peyers patch immunization of killed *H. pylori* in rats shows that the gut mucosa can mount a vigorous immune response, oral immunization with either live or killed bacteria induced no significant serum or salival antibody response (Dunkley, M, Australia). Blaser also warned that because of the possible autoimmune component of the disease the wrong vaccine could actually make things worse."

Unfortunately, the vaccine art is replete with instances where even well characterized immunogenic agents that induce a neutralizing antibody, defined by in vitro assay, fail to elicit in vivo protective immunity (Boslego). Merely because an immune

response can be stimulated to a Helicobacter immunogenic agent, does not define the immunogenic agent as an agent for preventing or treating Helicobacter infection. Accordingly, the art indicates that it would require undue experimentation to formulate and use a successful immunogenic agent vaccine without the prior demonstration of vaccine efficacy.

It is known it the art that vaccines convey protection from infection and disease. Rappuoli et al (European Journal of Gastroenterology and Hepatology, 1993, Vol.5, (suppl. 2) pages 576-578) teach that development of a vaccine against *Helicobacter pylori* would involve four major steps:

1) identification of the factors required for virulence;

2) large-scale production and characterization of the virulence factors;

3) development of appropriate animal models to test the virulence and immunogenicity of the molecules identified; and

4) identification of the type of immunity able to prevent infection and disease.

No art recognized *in vitro* or *in vivo* models are showing how any single immunogenic agent would result in prevention of infection or disease. No examples containing the missing information has been provided.

Given the lack of guidance on how to obtain the desired effect using an immunogenic agent comprising any immunogenic

agent in a method of treating or preventing *Helicobacter* infection, and in light of the teachings of the prior art which teach that vaccines comprising Helicobacter antigens are unpredictable in methods of treating or preventing infection the skilled artisan could not make and use the claimed invention. No working examples are shown which convey the missing information. Therefore, the skilled artisan could not use **any** Helicobacter immunogenic agent to obtain the desired effect of preventing or treating infection without undue experimentation.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1, 2-4, 6,7-9 and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claimed immunogenic agent derived from Helicobacter that will induce the recited ratios of antibodies (claims 2-4 and 7-9) does not distinctly claim Applicant's invention in view of the fact that polyclonal antibodies in a host are not predictably produced to the same level in the same animal or between animals

(see section 1.2.1, Campbell, Laboratory Techniques in Biochemistry and Molecular Biology, page 3). What the immunogenic agent is, in view of the functional limitations is not clearly pointed out.

The recitation of ratios where the IgG1 titer is greater than the IgG2 titer is confusing, in view of the base claim defining the immune response is intended to induce a predominant Th1 (IgG2) immune response (claims 1 and 6). The inventions are defined by a ratio of **IgG2a** : **IgG1** titers (see claims 2-4 and 7-9). IgG1 (Th2) is claimed as the predominant immune response through the recitation of the ratio of IgG1 titer being 100, 10 or 2 times greater than the IgG2 immune response (1 part IgG2 to 100 parts IgG1 (1:100)). The dependent claims recite the predominant immune response induced is a Th2 immune response (claims 2-4, 7-9), not a Th1 immune response as defined in the base claim. The immunogenic agent is not distinctly claimed because the claim limitations recited are apparently contradictory (see page 5,lines 8-13; page 3, lines 6-8). Clarification is requested.

9. Claims 1-18 provides for the use of an immunogenic agent, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely

recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 1-18 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 U.S.C. § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

Please Note: Claims 1-18, that recite an intended use of an immunogenic agent derived from Helicobacter, are being read as composition claims.

11. Claims 1-18 are rejected under 35 U.S.C. 102(b) as being anticipated by **Guy et al** (WO96/31235 in light of Guy et al (US Pat. 6,126,938 (English translation of WO96/31235)).

Guy et al disclose and claim Helicobacter pylori agents, specifically an Helicobacter apoenzyme immunogenic agent (see claims 21-22, page 40), for the induction of an immune response through mucosal and parenteral administration. Guy et al anticipates the now claimed immunogenic agents with the recited intended uses.

12. Claims 1-18 are rejected under 35 U.S.C. 102(e) as being anticipated by **Morrow et al** (US Pat 5,817,512) in light of Novak (1999).

The claimed invention is directed to immunogenic agents of Helicobacter.

Morrow et al disclose and claim encapsulated recombinant poliovirus compositions that comprise a Helicobacter pylori

nucleic acid sequence (see claim 13 and 31) and teaches the use of a coding sequence for Helicobacter pylori urease nucleic acid (see col. 9, line 11). Both parenteral and mucosal methods of administration are disclosed for the encapsulated viral/Helicobacter compositions (see col. 15, lines 45-64).

Inherently the composition would induce a Th1 associated immune response (Novak), and therefore anticipates the now claimed invention.

13. Claims 1-18 are rejected under 35 U.S.C. 102(e) as being anticipated by **Holmgren** et al (US Pat 6,153,203).

The claimed invention is directed to immunogenic agents of Helicobacter .

Holmgren et al disclose and claim the use of an immunogenic agent that comprises a Helicobacter pylori specific antigen (see claims 1,5,and 6)linked to either cholera toxin B subunit or Escherichia coli heat labile enterotoxin B subunit.

Inherently the composition would induce the desired Th1 immune response and therefore anticipates the now claimed invention.

Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594

14. Claims 1-18 are rejected under 35 U.S.C. 102(e) as being anticipated by **Marciani** (US Pat 6,080,725).

The claimed invention is directed to immunogenic agents of Helicobacter.

Marciani discloses and claims the use of an immunogenic agent that comprises a Helicobacter pylori specific antigen (see claims 11) together with a pharmaceutically acceptable carrier (see claim 1) with the intended use of obtaining a potentiated immune response.

Inherently the composition would induce the desired Th1 immune response and therefore anticipates the now claimed invention.

Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594

15. Claims 1-18 are rejected under 35 U.S.C. 102(b) as being anticipated by **Mohammadi et al** (The Journal of Immunology, Vol. 156, pages 4729-2738, 1996).

The claimed invention is directed to immunogenic agents of Helicobacter.

Mohammadi et al disclose a Helicobacter pylori immunogenic agent that was formulated together with a pharmaceutical carrier, $NaHCO_3$, and an adjuvant amount of cholera toxin. The immunogenic agent was used in a method of inducing an immune response, which induced a predominantly Th-1 type, Ag-specific response (abstract, last two lines, page 4729).

Inherently the immunogenic agent of the prior art anticipates the now claimed immunogenic agent.

16. Claims 1-10 are rejected under 35 U.S.C. 102(b) as being anticipated by **Pappo et al** (Infection Immunity, April 1995).

The claimed invention is directed to immunogenic agents of Helicobacter.

Pappo et al disclose Helicobacter pylori immunogenic agents, (H.felis sonicate or recombinant urease: UreA and UreB) that were formulated together with an adjuvant amount of cholera toxin (see page 1247, col. 1, paragraph 3). The immunogenic agents were used in a method of inducing an immune response, which induced a distribution of leukocytes (see Table 2) to include CD4 leukocytes that are known to be associated with Th1 immune responses. The compositions are inherently the immunogenic agents now claimed. Pappo et al anticipate the instantly claimed invention.

Inherently the immunogenic agent of the prior art anticipates the now claimed immunogenic agent.

17. Claims 1-10 are rejected under 35 U.S.C. 102(b) as being anticipated by **Telford et al** (Drugs, 1996).

The claimed invention is directed to immunogenic agents of Helicobacter.

Telford et al disclose Helicobacter pylori CagA protein as a dominant immunogenic agent that induces a Th1 (T-helper type 1) immune response (see page 800, col. 2, paragraph 3, second half of paragraph). Inherently, CagA, the immunogenic agent of the prior art, anticipates the now claimed immunogenic agent.

Claim Rejections - 35 U.S.C. § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Guy et al (WO96/31235) in light of Guy et al (US Pat. 6,126,938 (English translation of WO96/31235)).

Guy et al disclose a method of inducing an immune response for preventing or treating infection comprising mucosally and then parenterally administering the antigen to the host. (See page 14, lines 40-41 and page 15, lines 1-3 which corresponds to US Pat. 6,126,938: col. 7, lines 44-50) (also see page 8, lines 5-11 which corresponds to US Pat. 6,126,938: col. 3, lines 32-40).

The reference teaches the formulation and use of an immunogenic agent that comprises Helicobacter pylori antigen (see page 15, lines 34-37 and page 16, lines 5-8, which to US Pat. 6,126,938: col. 8, lines 17-27).

The method is a method of inducing a mucosal immune response through mucosal administration to the nasobuccal route combined with the subsequent administration ~~of~~ or systemic administration of the immunogenic agent. The reference teaches that the combinations of oral/subcutaneous and subcutaneous/oral have been shown to be effective means for induction of a mucosal immune response and exemplifies the subcutaneous/oral route for induction of an immune response (see page 8, lines 5-11 which corresponds to US Pat. 6,126,938: col. 3, lines 32-40) and claims the use of immunogenic agents for systemic and oral administration (see page 38-40, claims 1, 3, 19,21 and 22). The reference differs from the instantly claimed invention by failing

to show the method using mucosal followed by parenteral administration for induction of an immune response against a Helicobacter pylori immunogenic agent as taught.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to administer an immunogenic agent that comprises Helicobacter pylori antigen by the mucosal route followed by the parenteral route for the induction of a protective immune response because Guy et al teach the use of Helicobacter protective antigens (urease, see page 40, claim 22) and that this method has been shown to be effective by Forest (see page 8, lines 5-11 which corresponds to US Pat. 6,126,938: col. 3, lines 32-40) against a mucosal pathogen, Salmonella, and Guy teaches that an effective immune response against pathogens that infect the stomach (Helicobacter) and intestine can be obtained through administration of an antigen composition in a method that combines both the mucosal and parental routes of stimulating an immune response.

In the absence of a showing of unexpected results, Guy et al obviate the now claimed method.

Conclusion

20. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure, some of which are cumulative to the applied references above.

21. Bamford et al (1996) is cited to show the relative numbers of CD3+, CD4+ and CD8+ cells which produce TH1 type cytokines in Helicobacter pylori gastritis.

22. Bowen et al (1994) is cited to show cholera toxin to be a strong system and mucosal adjuvant.

23. Crowe et al (1996) is cited to show Helicobacter pylori and cytokines from gastric TH1 cells induce apoptosis in gastric epithelium.

24. Calenoff (WO92/19970) is cited to show a method of inducing immune tolerance in a mammal using Helicobacter pylori antigens.

25. Corthesy-theulaz et al (Feb. 1998, abstract) is cited to show the use of an attenuated Salmonella for the expression of Helicobacter urease A and B subunits in a mammal.

26. Covacci et al (WO93/18150) is cited to show a method of preparing a pharmaceutical composition (see claims 19) using various cytokine and interleukin adjuvants (see page 40, paragraphs 1-5).

27. Chen et al (1993) is cited to show intraperitoneal injection of an immunogenic agent that comprised Helicobacter antigen.

28. D'Elios et al (1997) is cited to show TH1 effector cells are present in the gastric antrum of patients with peptic ulcer disease.

29. Doidge et al (WO95/33482) is cited to show the use of a non-toxic derivative of cholera toxin as an adjuvant with Helicobacter immunogenic agents (catalase, page 7, paragraph 1).

30. Guy et al (May 1998) is cited to show systemic immunization with urease protects mice against Helicobacter pylori infection.

31. Hornquist et al (1993) is cited to show cholera toxin as a potent adjuvant for both Th1 and Th2 immune responses.

32. Lee et al is cited to show the induction of an immune response by subcutaneous administration of antigen.

33. Michetti et al (WO94/09823) is cited to show the administration of Helicobacter antigen through transport across epithelium (see claim 19).

34. Mohammadi et al (1996) is cited to show Helicobacter specific cell mediated immune responses display a predominant Th1 phenotype and promote a delayed type hypersensitivity in the stomach of mice.

35. Saldinger et al (1997) is cited to show strong Th1 immune responses are induced in mice when immunized with Helicobacter antigens.

36. Varga Laszlo (1992) is cited to show human immunization with Helicobacter antigens.

37. Corthesy-theulaz et al (1998) is cited to show the induction of a protective immune response to Helicobacter antigen delivered through the use of a Salmonella host cell.

38. Mohammadi et al (1996) is cited to show that a Th1 immune response exacerbates the magnitude of infection.

39. Ward et al (US Pat. 5,610,060) is cited for teaching the sublingual administration of Helicobacter antigen (see col. 4, line 51).

40. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be Group Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this Art Unit.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vgp February 21, 2001

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